REMARKS

I. Claim Amendments

Applicants have amended the claims pending in this application to better define the invention over the prior art. Claims 1 and 7 have been amended to specify that individual cells within the claimed composition or obtained by the claimed method are capable of differentiation into T-, B- or NK-cells, but not myeloid cells. Specifically, claims 1 and 7 have been amended to recite that "an individual progenitor cell in said [common lymphoid progenitor cell] composition is capable of giving rise to each of T cells, B cells and natural killer cells, but not myeloid cells." It is this feature -- the identification and demonstration of a single common progenitor for T-, B- and NK-cells -- that renders the present invention novel and non-obvious over the prior art.

Applicants have also added claims 19-22, which further embody the invention. Claim 19 recites "an isolated mammalian hematopoietic cell characterized as c-kit^{lo}, IL-7Rα^{+}, lin^{-}, wherein said cell is capable of differentiating into T cells, B cells and natural killer cells, but not into myeloid cells." Claims 20-22 depend from claim 19 and recite that the cell has the additional cell surface marker characteristics Thy-1^{-} (claim 20); Sca-1^{lo} (claim 21); and CD43^{lo}, HSA^{lo}, CD45^{+} and MEL-14^{-} (claim22).

Support for these amendment and added claims is found in the specification, wherein experiments demonstrate that a single cell obtained by limiting dilution (page 18, line 24 – page 19, line 20) or by isolation and expansion in methyl cellulose (page 20, line 17 – page 21, line 5) was capable of reconstituting B- and T- cells, but not myeloid cells, when injected into a mouse. None of these amendments present new matter.

II. Rejections

The Examiner asserts that the specification lacks an abstract of the disclosure as required by 37 C.F.R. §1.72(b). Page 27 of the originally filed application was an Abstract of the Disclosure. Applicants received a stamped post card receipt confirming that the originally filed application contained 27 pages (see attached). Therefore, applicants respectfully submit that the Examiner has either overlooked page 27 of the application as originally filed or that this page has been lost by the Patent Office. For the convenience of the Examiner, applicants have attached a duplicate copy of page 27. That page is an Abstract of the Disclosure.

The Examiner contends that the application fails to comply with 37 C.F.R. §§1.821-1.825 for failure to submit a Sequence Listing in computer readable form (as indicated on the Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures). Applicants have obviated this requirement by submitting

herewith a computer readable form ("CRF") copy of the Sequence Listing and a Statement Under 37 C.F.R. §1.821(f) that the CRF is identical to the paper copy of the Sequence Listing contained on pages 21-22 of the originally filed application.

Claims 1-3 and 6-10 stand rejected under 35 U.S.C. §103 as being unpatentable over Olweus et al. (US 6,555,324) in view of Galy (US 5,972,627). Specifically, the Examiner asserts that Olweus et al. teach that "progenitors committed to lymphoid lineage" can be identified by the "marker IL-7R" and that Galy teach that such cells are Lin^-, $Thy\text{-}1^-$, $c\text{-}kit^{low}$. Thus, the Examiner concludes that it would have "been obvious to one of skill in the art at the time the invention was made to modify the methods taught by Olweus et al. by combining $CD34^+/CD38^+$ positive selection with lineage marker-negative selection as taught by Galy, followed by the IL-7R selection for identifying and enrichment of lymphoid progenitor cells with a reasonable likelihood of success." Applicants traverse based upon the amendments presented herein.

In assessing the disclosures of both Olweus et al. and Galy, it is important to note that neither reference demonstrates the existence of a single common lymphocyte progenitor cell. One of ordinary skill in the art would not have been provided with a reasonable expectation that the cell populations described in either of those documents contained individual cells which could give rise to any of B-, T- or NK-cells. This is because neither of those patents provides any experimental evidence of such a common lymphoid progenitor cell.

Galy demonstrates that a population of $CD45^+RA^+CD10^+Lin^-CD34^+$ cells can give rise to T- B- and NK-cells (and dendritic cells). However, this same result would be obtained if such population is a mixture of unipotent T- B- and NK-cell progenitors, as opposed to a population of multipotent progenitors, wherein each progenitor could give rise to all three lymphoid cell types. This possibility is confirmed in K. Shortman and L. Wu, "Early T Lymphocyte Progenitors," Ann. Rev. Immunol., 14, pp. 29-47 (1996; copy enclosed), wherein the authors state:

> "Recent extensions of these studies by Galy and colleagues (AHM Galy, personal communication) have led to the identification of a 'lymphoid progenitor' population with a capacity to form T cells, B cells, natural killer (NK) cells, and interdigitating dendritic cells (DC), but not to form normal myeloid, erythroid, or megakaryocytic cells. This suggests development within the bone marrow of a common lymphoid progenitor, if the term can be extended to include certain DC. However, clonal studies will be required to eliminate the possibility that the population is a mix of individual unipotent progenitors (either T, or B, or NK or DC committed) with identical surface phenotype." (emphasis added, p. 33).

Galy did not demonstrate possession of a composition of mammalian common lymphoid progenitor cells, wherein an individual progenitor cell in said composition is capable of giving rise to each of T cells, B cells and natural killer cells, but not to myeloid cells. Nor did Galy

isolate a mammalian hematopoietic cell characterized as c-kit^{lo}, IL-7Rα^{+}, lin^{-}, wherein said cell is capable of differentiating into T cells, B cells and natural killer cells, but not into myeloid cells.

Olweus et al. fails to provide any information or data to cure the shortcomings of Galy. In fact, Olweus et al. fails to provide any evidence that its cell population of "progenitor cells committed to the lymphoid lineage" can, in fact, give rise to B-, T- and NK-cells, much less distinguishing between the possibilities of a mixed population of unipotent lymphoid progenitors and a population of individual multipotent lymphoid progenitors[1]. There is not a single experimental example in Olweus et al. that demonstrates its "progenitor cells committed to the lymphoid lineage" can actually give rise to any of B-, T- or NK-cells, much less that any single cell in that population could give rise to all three lymphoid cell types.

Thus, even if one of skill in the art were motivated to combine the IL-7Rα^{+} marker of the Olweus et al. cell population with the c-kit^{lo} and lin^{-} markers of the Galy cell population, there would be no expectation of applicants' invention -- that a single cell characterized by such markers would be able to give rise to all of B-, T- and NK-cells. Similarly, there would be no expectation that a population of cells characterized by those markers would contain a single cell that could give rise to all of B-, T- and NK-cells. It was not until the present applicants demonstrated that single cells in a c-kit^{lo}, IL-7Rα^{+}, lin^{-} population could reconstitute B-, T- and NK-cells in a sublethally irradiated mouse that the art could be reasonably assured of the existence of a common lymphoid progenitor cell. The amended claims presented herein specifically recite this inventive feature and are therefore patentable over the combination of Galy and Olweus et al.

Applicants note that there are clinical advantages to the use of a common progenitor cell, rather than a mixture of unipotent cells. During the differentiation of lymphocytes, there is step-wise narrowing of differentiation potential, from hematopoietic stem cell to common progenitor cells, to pro-T cells and pro-B cells, and to fully differentiated B and T cells. During differentiation, lymphocytes rearrange the genetic sequences encoding their respective antigen receptors, resulting in a loss of genetic information, and a narrowing of potential rearrangements. The use of more differentiated cells may limit the diversity of T cell receptor

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[1] It is interesting to note that applicants have been unable to identify a single scientific article authored by any of the inventors listed on the Olweus et al patent and published between the filing dates of Olweus et al. and the present application that identifies or suggests that the IL-7Rα^{+} marker is indicative of a common lymphocyte progenitor cell.

and immunoglobulins that can be rearranged and displayed by the cells as they mature, thus resulting in a more limited repertoire available for fighting infection and disease.

Claims 1-4 and 6-11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Olweus et al. and Galy in view of Kawamoto et al. Specifically, the Examiner asserts that Kawamoto et al. teach that a Sca-1$^-$ population only give rise to one of the T, B or M cells and that "commitment to the M lineage begins at the Sca-1$^+$ stage, whereas commitment to the B lineage occurs after losing the Sca-1 antigen." The Examiner concludes that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by Olweus et al and Galy by simply including Sca-1 as one of the markers for the enrichment of lymphoid progenitor cells, with a reasonable expectation of success." Applicants traverse.

As explained above, the claims in the present application have been amended to specifically recite that an individual cell in applicants' c-kit^{lo}, IL-7Rα^+, lin$^-$ (Sca-1^{lo}) population can give rise to each of T- B- and NK-cells, but not myeloid cells. The primary combination of references cited by the Examiner do not make obvious this claimed invention because they fail to teach or provide a reasonable expectation of the existence of such a multipotent common lymphoid progenitor cell. Kawamoto et al. does not provide anything to remedy this failure. In fact, Kawamoto et al. supports the present applicants' position that there was no reasonable expectation of the existence of a multipotent common lymphoid progenitor cell in the art prior to the present invention.

Kawamoto et al. states that "[I]n the Sca-1$^-$ population, all progenitors detected were unipotent, suggesting that the process of T, B and M lineage commitment has finished during the Sca-1$^+$ stage" (page 1015, right column). This contradicts the Examiner's suggestion that "[t]he ordinary skilled artisan would have been motivated to modify the method [suggested by the combination of Olweus et al and Galy] because Sca-1^{lo} could eliminate some of the myeloid progenitor cells (a negative selection process as taught by Galy) while permit[ting] the lymphoid progenitors [to] remain in the population." The results of Kawamoto et al. do not in any way relate to a Sca-1^{lo} population because that reference never identified such a population. What is clear from Kawamoto et al. is that multipotent cells are only found in the Sca-1$^+$ population, while all Sca-1$^-$ cells are unipotent (see Figure 5, page 1017). The results of Kawamoto et al do not provide one of skill in the art with any teaching of suggestion that a Sca-1^{lo} population would contain cells that could give rise to lymphoid, but not myeloid progeny.

Significantly, even in the Sca-1$^+$ population Kawamoto et al. was unable to detect any bipotent cells capable of differentiating into both T- and B-cells (termed "p-TB"), leading the authors to state: "So far it is unclear whether or not p-TB type progenitors exist... Further investigation is necessary to clarify whether the development of T and B cells progresses through a common route" (page 1018, left column). This statement is consistent with the uncertainty in the art prior to the effective filing date of the present application as to the existence on a true common lymphocyte progenitor cell. It is only in light of applicants' invention that the art was provided with the requisite reasonable expectation of the existence of such a cell. That invention, which is embodied in the amended and added claims presented herein, is not obvious over the combination of Olweus et al., Galy and Kawamoto et al. or any other combination of prior art of which applicants are aware. Accordingly, applicants request that the Examiner withdraw this §103 rejection.

Claims 1-3 and 5-10 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Olweus et al. and Galy further in view of Kincade et al. and Ballas et al. In particular, the Examiner asserts that "Kincade et al teach selective regulation of B lymphocyte precursor (lymphoid progenitor) cells by targeting CD45RA, CD43, IL-7 and heat stable antigen (HSA, column 10, lines 3-9)" and that "Ballas et al. teach that thymocytes are MEL-14$^-$, whereas mature peripheral NK cells are MEL-14$^+$." Therefore, the Examiner concludes that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by Olweus et al and Galy by simply including CD43^{lo}, HSA^{lo}, and Mel-14$^-$ as markers for the enrichment of lymphoid progenitor cells, with a reasonable expectation of success." The Examiner contends that the motivation for such a combination would be because these "additional markers serve to verifying [sic, verify] whether the selected cell population is enriched of lymphoid progenitor cells or contaminated with mature lymphocytes." Applicants traverse this rejection.

Initially it should be pointed out that distinguishing between an enriched population of lymphoid progenitor cells and contamination with mature lymphocytes falls far short of the present invention. Applicants' invention is not concerned with any enriched population of lymphoid progenitor cells. Rather, applicants invention is directed to isolating a composition of <u>common</u> lymphoid progenitor cells wherein "an individual progenitor cell in said composition is capable of giving rise to each of T cells, B cells and natural killer cells, but not to myeloid cells." That claimed cell population should be essentially free of more lineage-committed lymphoid precursors, such as thymocytes and B-cell precursors.

As discussed above, the primary combination of references, Olweus et al. and Galy, do not render such a composition obvious. The secondary references, Kincade et al and Ballas et al., describe certain cell surface markers that distinguish individual mature lymphocytes of a specific type (B-cell or NK-cell) from their earlier stage unipotent precursor. That precursor is not the same as the multipotent progenitor being claimed by applicant. There is no teaching or suggestion in Kincade et al. or Ballas et al. as to the expression level of CD43, HSA, and Mel-14 in a common lymphoid progenitor, much less whether such a common lymphoid progenitor cell even exists. As such, one of ordinary skill in the art would not be motivated to combine the unipotent cell surface markers referred to in those secondary references with the markers that characterize the cell populations of Galy and Olweus et al. in order to isolate the presently claimed multipotent lymphoid progenitor or a composition comprising that progenitor.

Moreover, even if one of skill in the art were to combine the teachings of Olweus et al., Galy, Kincade et al. and Ballas et al., that combination would fall short of providing the requisite reasonable expectation of successfully isolating applicants' multipotent common lymphoid progenitor. Kincade et al. teaches that "very early B-lymphocyte precursors are TdT^+, $CD45R^+$, HSA^{lo}, $CD43^+$," that "Pro-B and large pre-B lymphocyte precursors are $CD45R^+$, HSA^{hi}, $CD43^+$," and that "Small pre-B lymphocyte precursors are $CD45R^+$, HSA^{hi}, $CD43^-$." Even assuming one of skill in the art seeking cell surface characteristics of a common, multipotent lymphoid progenitor would turn to Kincade et al. (which they would not), there is nothing in that patent to suggest that such a progenitor would be HSA^{lo}, $CD43^{lo}$. For example, if one assumed that the presently claimed common lymphoid progenitor was farther upstream in terms of commitment from Kincade et al.'s very early B-lymphocyte precursors, Kincade et al.'s data would not allow one to predict whether that progenitor would be HSA^{lo} or HSA^-, based upon the trend of HSA expression shown for B-cell development. The trend of CD43 expression through B-cell development demonstrated by Kincade et al. suggests that progenitors upstream from very early B-lymphocyte precursors would be $CD43^+$ or CD 43^{hi} because more mature B-cell precursors lose CD43 expression. This prediction would be incorrect. Applicants' common multipotent lymphocyte progenitors are $CD43^{lo}$. Thus, Kincade et al., actually teaches away from applicants' invention and would not lead one of skill to the proper characterization of CD43 expression in such a common progenitor.

Ballas et al. does not relate to HSA or CD43 expression and therefore could not overcome the problems inherent in using Kincade et al. to predict the expression of those cell surface markers in a common lymphocyte progenitor. Accordingly, the combination of Olweus et al., Galy, Kincade et al. and Ballas et al. would not render obvious applicants' claimed

hematopoietic cell characterized as c-kit^{lo}, IL-7Rα^{+}, lin^{-}, CD43^{lo}, HSA^{lo}, CD45^{+} and MEL-14^{-}, wherein said cell is capable of differentiating into T cells, B cells and natural killer cells, but not into myeloid cells (claim 22), or a composition containing such a cell (claim 5). Therefore, applicants request that the Examiner withdraw this rejection.

III. Conclusion

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number STAN-064.

Respectfully submitted,

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